Remarks

Amendments:

Claims 2, 10-14, 40-51, 55-76, 86, 87, 95-97 and 99-106 are cancelled. Applicants expressly reserve the right to file one or more continuing applications on the subject matter of the cancelled claims.

Claims 1, 3, 16-18, 22-33, 52-54, 77, 85, 88-94 and 98 are amended.

Claim 1 is amended to include the limitation of previously pending and now cancelled claim 14. Claims 1 and 77 are amended to include a size limitation for the nucleic acid. Support for this amendment can be found on page 4, lines 15-17.

Claims 3, 52 and 53 are amended to correct dependency.

Claims 16-18, 22-33, 77, 85, 88-94 and 98 are amended to recite correct antecedent basis.

Claim 53 is amended to include additional subject types. Support for this amendment can be found in the specification on page 17, lines 30-32 and in previously pending and now cancelled claim 59.

Claim 54 is amended to correct the meaning of ADCC. Support for this amendment can be found in the specification on page 101, line 24 (along with the knowledge in the art).

Claims 107-112 are added. Support for these claims can be found in the claims as originally filed (see for example claim 35 (supporting new claim 107), claim 54 (supporting new claim 108), claim 57 (supporting new claim 109) and claim 77 (supporting new claim 112)), and throughout the specification including page 5, lines 8-10 and page 30, lines 5-9.

No new matter has been added.

Claims 1, 3-9, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 are pending.

Election/Restriction:

Applicants acknowledge the Examiner's withdrawal of the restriction requirement between Groups 1, 3, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Withdrawn claims 40-44 and 62-73 are cancelled herewith.

Objection to the Specification:

The specification is objected to for not including U.S. Patent numbers for recited patent applications. The specification is amended to recite U.S. Patent numbers for cited references, where appropriate. Applicants request that the objection be withdrawn.

Objections to the Claims:

Claims 1, 59, 76-77, 86 and 88-89 are objected to for various informalities.

Claims 1 and 77 are amended to remove the recitation of TG-nucleic acids. Claim 76 is cancelled.

Claim 59 is cancelled.

Claim 86 is cancelled. Claims 88 and 89 are amended.

Applicants request that the objection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph:

Claims 11-15, 61, 85 and 98 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-14 are cancelled. In view of the amendment to claim 1, claim 15 finds sufficient antecedent basis in claim 1.

Claim 61 is cancelled.

Claim 85 is amended to recite "poly T nucleic acid motifs" rather than "T motifs".

Claim 98 is amended to recite that poly T nucleic acid motifs are interspersed with CpG motifs.

Applicants request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph, enablement:

Claims 1-16, 18-24, 26-39, 45-61, 74-77, 85-94 and 98 are rejected under 35 U.S.C. § 112, first paragraph because according to the Examiner the specification does not reasonably enable:

(i) a method of stimulating an immune response and an innate immune response in a non-rodent subject comprising administering a non-CpG Py-rich or non-CpG T-rich immunostimulatory nucleic acid,

(ii) a method of stimulating an immune response comprising administering a polycytosine homopolymer or a polythymidine homopolymer shorter than 21 nucleotides, and

(iii) a method for treating or preventing asthma, allergy, infectious disease, and cancer comprising stimulating an immune response in a non-rodent subject comprising administering a CpG or non CpG Py-rich or T-rich immunostimulatory nucleic acid, wherein the cancer treatment further comprises administering an anti-cancer therapy selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent and a cancer vaccine.

The Examiner acknowledges that the specification enables a method of stimulating an immune response and an innate immune response comprising administering a CpG containing Py-rich or T-rich immunostimulatory nucleic acid. The Examiner however also states that the specification is further "enabling for a method of stimulating an immune response comprising administering a Py-rich or T-rich immunostimulatory nucleic acid" (see present office action, page 6, lines 2-4). This statement appears inconsistent with enablement basis (i) recited above (see present office action, page 6, lines 6-9). The Examiner is asked to clarify the inconsistency for the record.

At the outset, Applicants point out that claim 1 is amended to recite immunostimulatory nucleic acids that are T-rich immunostimulatory nucleic acids. Accordingly, the enablement rejection based on polycytosine homopolymers is moot. Applicants have further cancelled claims 45-48, 50, 51, 75 and 76, and thus enablement basis (iii) recited above is moot also.

Applicants traverse the remaining rejection for the reasons set forth below.

The enablement requirement is satisfied if one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation. The experimentation required to make and use the claimed invention may be complex, and still not undue, if the art routinely engages in that level of experimentation.

The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of

experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive of the issue of enablement. Applicants analyze each factor below in the context of the claimed invention.

Nature of the invention: The invention relates in part to the finding that T-rich nucleic acids can be immunostimulatory. T-rich nucleic acids embrace nucleic acids having greater than 25% T content and/or a poly T motif (i.e., 4 contiguous T nucleotides). Such nucleic acids are immunostimulatory independent of their CpG content. These nucleic acids are capable of stimulating B cells, activating NK cells (and thereby enhancing NK-mediated cytotoxicity) and NKT cells, stimulating monocytes, and inducing release of TNFα and IL-6 in PBMC cultures.

Breadth of the claims: The claims relate to methods of stimulating immune responses in non-rodent subjects by administering T-rich immunostimulatory nucleic acids that are 8-100 nucleotides in length. The immune responses may be systemic immune responses and/or they may be ADCC-mediated immune responses. Some methods require that the T-rich immunostimulatory nucleic acid have a nucleotide composition of at least 60% thymidine (T) which may optionally contain a CpG motif.

State of the prior art at the time of filing: The state of the art at the effective filing date is reflected at least in part in the Background section of the instant specification. The art was aware of CpG nucleic acid motifs that impart immunostimulatory properties to nucleic acids. The ability to make oligonucleotides in general and to use CpG immunostimulatory oligonucleotides in particular was also known at the time of effective filing. In vitro immunostimulation assays (and their relevance to in vivo efficacy) were also known and appreciated.

Level of ordinary skill in the art: The level of ordinary skill in the art is at least that of a molecular biologist. Molecular biologists would know how to synthesize and/or harvest nucleic acids described by the claims. Such artisans would consider this type and level of experimentation routine. Ordinary artisans might also include medical practitioners who prescribe or administer agents to subjects including human subjects. The level of ordinary skill is therefore high based on the education and training of persons expected to practice the claimed invention.

Level of predictability in the art: As of the effective filing date, the art with respect to nucleic acid synthesis or harvest and isolation of nucleic acids was routine and predictable. The

art routinely used automated nucleic acid synthesizers to generate nucleic acids of particular sequences and backbones. The art was also familiar with the ability to induce immune responses in vivo using immunostimulatory nucleic acids having CpG motifs.

The Examiner states that immune stimulation by nucleic acids shorter than 21 nucleotides is not enabled. However, Applicants direct the Examiner's attention to Example 6, pages 135 and 136 and Figure 5 which demonstrate that T-rich nucleic acids of 18 nucleotides stimulate B cells at least at doses of 1 and 10 μg/ml. The Examiner further highlights Example 12 which states that "immunostimulatory activity of ODN without CpG motifs ... was negative or weak compared to CpG ODN". Applicants wish to point out that Example 12 appears to have been performed with a single dose of nucleic acid (i.e., 0.2 μM ODN) and at *that dose* non-CpG nucleic acids including T-rich nucleic acids were characterized as negative or weak. However, as demonstrated in Figure 5, some T-rich nucleic acids are immunostimulatory at higher doses. Thus, while the non-CpG nucleic acids described in Example 12 were "negative or weak" at the doses used, this says nothing about their immunostimulatory ability at higher doses.

The Examiner cites Vollmer et al. (Antisense & Nucleic Acid Drug Development, 2002, 12:165-175) as teaching that "thymidine content and the length of a phosphorothioate-ODNs determine the immunostimulatory potential" and that "a short polythymidine ODN with 18 nucleotides showed background activity". Applicants maintain that the results of Vollmer et al. are dosage specific and that for every T-rich nucleic acid there is an optimal dose which may not be reflected in the data of Vollmer et al. The Examiner is directed to Fig. 1 of Vollmer et al. which shows immunostimulation by a T-rich nucleic acid that is 17 nucleotides in length (ODN 5192). The dose-response data for this nucleic acid demonstrate that its stimulatory capacity increases substantially with increasing dose. The data highlighted by the Examiner in Fig. 2 corresponds to a *single* dose and there is no indication that it is necessarily the optimal dose for the nucleic acids tested. Thus, the teaching that "a short polythymidine ODN with 18 nucleotides showed background activity" should be qualified to the dose tested.

Similarly, the data of McCluskie et al. (Vaccine, 2001, 19:2657-2660) correspond to only one dose of a single T-rich nucleic acid. Presumably, it is a dose at which CpG nucleic acids perform well. However, as argued herein, that dose may not be optimal for a non-CpG nucleic acid such as a non-CpG T-rich nucleic acid. Applicants note that the specification teaches that the optimal immunostimulatory doses for non-CpG T-rich nucleic acids actually result in

decreased activity for CpG nucleic acids. This observation supports the idea that the McCluskie et al. data correspond to optimal CpG nucleic acid doses that are not necessarily optimal non-CpG T-rich nucleic acid doses. The teaching of Jones et al. (Vaccine, 1999, 17:3065-3071) can be similarly qualified since only a single dose of nucleic acid was used and that dose was clearly optimized for CpG nucleic acid effect. Vollmer et al., McCluskie et al. and Jones et al. therefore stand for the proposition that higher doses of non-CpG T-rich nucleic acids may be necessary for immune stimulation (as compared to optimal CpG nucleic acids). They do not stand for the proposition that short T-rich nucleic acids are not immunostimulatory, as asserted by the Examiner.

Amount of direction provided by the inventor: The specification teaches the parameters of the nucleic acids to be used in the claimed methods. The specification demonstrates that T-rich nucleic acids are capable of immune stimulation in vitro, independent of their CpG content. The specification teaches administration of these nucleic acids to non-rodent subjects including formulations, administration routes and effective amounts. (See for example page 20, lines 1-27, page 62, lines 24-30, page 63, lines 20-32, page 64, lines 25, page 79, lines 27-32, page 80, lines 1-16, page 99, lines 18-31, page 100, lines 1-2, and pages 117-123.) In this latter regard, MPEP § 2164.01(c) states that "if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." (citing In re Johnson 282 F.2d 370, 373 (CCPA 1960).) Accordingly, the amount of direction provided by the inventors is considered sufficient, particularly in view of the level of ordinary skill in the art.

Working examples: The specification provides a number of in vitro assays demonstrating the immunostimulatory properties of T-rich nucleic acids. For example, these nucleic acids are shown to stimulate B cells, NK cells, NKT cells and monocytes, and to induce the secretion of TNFα and IL-6 from human PBMC. The Examiner has highlighted much of this data (see present office action, page 7, lines 11-22). The ability to stimulate B cells and NKT cells correlates at least with a role in adaptive (or antigen-specific) immunity in vivo. The ability to stimulate NK cells correlates at least with a role in adaptive immunity and more particularly a role in ADCC in vivo. The ability to induce TNFα and IL-6 correlates at least with a role in innate immunity in vivo. The ability to stimulate monocytes correlates with a role in both types of immunity.

These immunostimulatory properties were not dependent upon the presence of CpG motifs, as also acknowledged by the Examiner (see present office action, page 7, lines 11-22). In still other instances, inclusion of a poly T motif or increase in T content enhanced the immunostimulatory capacity of a CpG nucleic acid. In some instances it was found that a higher dose of the non-CpG T-rich nucleic acid was necessary to achieve the desired result; however, this does not negate enablement since the nucleic acids were still shown to be immunostimulatory.

The Examiner asserts that "the specification does not teach any in vivo activity or in vivo immune stimulation associated with the administration of the Py-rich or T-rich ODNs lacking a CpG dinucleotide to non-rodent subject (e.g., human subject)". Applicants submit that the in vitro data presented in the specification is correlative to the claimed in vivo methods. The in vitro methods demonstrate the ability of T-rich nucleic acids to stimulate immune responses, particularly immune responses from human PBMC. The claimed in vivo methods require stimulation of an immune response in non-rodent subjects including humans.

The Examiner states that "in vitro ... studies have not correlated well with in vivo clinical trial results" and "it is not clear that reliance in the in vitro stimulation of immune cells ... accurately reflects the relative efficacy of the claimed therapeutic strategy". However, the Examiner has not provided any basis other than his own opinion to support these statements. As argued above, the in vitro activities are correlative with in vivo immune stimulation. For example, B cell and NKT cell activation are both associated at least with in vivo adaptive immunity. NK cell activation is associated at least with adaptive immunity and particularly ADCC. TNFα and IL-6 induction are associated at least with innate immunity. Monocyte activation is associated with both types of immunity and in some instances with ADCC. Furthermore, the Examiner is directed the CpG art which demonstrates that nucleic acids that function in the same in vitro assays as provided in the specification are capable of immune stimulation in vivo. This art evidences that in vitro assays such as those provided in the specification are predictive and thus correlative with in vivo immune stimulation, as presented claimed. Thus, the in vitro data should be considered as working examples.

Quantity of experimentation: The quantity of experimentation needed to make and use the invention, in view of the disclosure and the state of the art at the time of filing, is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art. The

specification provides the parameters that define a T-rich immunostimulatory nucleic acid both structurally and functionally, as well as species thereof. It further teaches how to formulate and administer the nucleic acids for immune stimulatory purposes.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 102(a):

Claims 1-13, 16-19, 21-22, 24-25, 37, 39, 77, 85-87, 90-92, 94 and 98 are rejected under 35 U.S.C. § 102(a) as being unpatentable over Jones et al. (Vaccine, 17:3065-3071, 1999).

Claim 1 has been amended to include the limitation of now cancelled claim 14 which was not rejected in view of Jones et al. New claims 107 and 108 find support in claims 35 and 54 which were not rejected in view of Jones et al. Accordingly, claim 1 as now amended and claims dependent thereon and new claims 107-109 are not anticipated by Jones et al.

Rejection under 35 U.S.C. § 102(e):

Claims 1-13, 16-19, 21, 24-25, 30, 33-34, 36-39, 77, 85-87, 94 and 98 are rejected under 35 U.S.C. § 102(e) as being anticipated by Krieg et al. (U.S. Patent 6,239,116 B1).

Claim 1 has been amended to include the limitation of now cancelled claim 14 which was not rejected in view of Krieg et al. New claims 107 and 108 find support in claims 35 and 54 which were not rejected in view of Krieg et al. Accordingly, claim 1 as now amended and claims dependent thereon and new claims 107-109 are not anticipated by Krieg et al.

Rejection under 35 U.S.C. § 102(b):

Claims 1-13, 16-21, 23-25, 30-31, 33-34, 36-39, 77, 85-87, 92, 94 and 98 are rejected under 35 U.S.C. § 102(b) as being unpatentable over Davis et al. (WO 98/40100).

Claim 1 has been amended to include the limitation of now cancelled claim 14 which was not rejected in view of Davis et al. New claims 107 and 108 find support in claims 35 and 54 which were not rejected in view of Davis et al. Accordingly, claim 1 as now amended and claims dependent thereon and new claims 107-109 are not anticipated by Davis et al.

Provisional Double Patenting Rejection:

Claims 1-5, 10-13, 16, 18-21, 25, 30-33, 36-39, 45-49, 52-61, 77, 85-87, 90, 94 and 98 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-58, 64-66, 71-74, 77-78, 80-81, 84, 89-90, 95-96 and 98 of copending U.S. application serial numbers 10/613,228, 10/613,739 and 10/613,736 in view of Krieg et al. (U.S. Patent 6,239,116).

Applicants wish to point out that the cited applications have a priority date after the priority date of the present application. Therefore, contrary to the Examiner's statement in the present office action, page 23, lines 17-20, these individual claimed sequences cannot anticipate the claimed genus of the present invention at least because they are not prior art to the present application. Applicants defer any further rebuttal of this rejection until it becomes final. In doing so, Applicants are not conceding the propriety of any of the Examiner's statements with respect to the cited and the present claims.

The present application is assigned to University of Iowa Research Foundation and Coley Pharmaceutical GmbH. The cited applications are assigned to Coley Pharmaceutical Group, Inc. The present and cited applications are therefore not co-owned. Applicants maintain that there is no conflicting subject matter between the present claims and those of the cited applications, and thus cannot name a prior inventor as requested by the Examiner.

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Claims 1-13, 16-20, 24-25, 30, 34-35, 37-39, 54, 56, 77, 85-87, 94 and 98 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5, 7-9, 16-18, 20-21, 23-25, 27-30, 34 and 40-41 of copending U.S. application serial number 10/272,502 in view of Krieg et al. (U.S. Patent 6,239,116).

Applicants wish to point out that the cited application has a priority date after the priority date of the present application. Therefore, the cited application is not prior art to the present application. Applicants maintain that the present claims are patentably distinct from the cited claims. Applicants defer any further rebuttal of this rejection until it becomes final. In doing so, Applicants are not conceding the propriety of any of the Examiner's statements with respect to the cited and the present claims.

The present application is assigned to University of Iowa Research Foundation and Coley Pharmaceutical GmbH. The cited application is assigned to University of Iowa Research

Foundation, Coley Pharmaceutical GmbH and Coley Pharmaceutical Group, Inc. The present and cited applications are therefore not co-owned. Applicants maintain that there is no conflicting subject matter between the present claims and those of the cited application, and thus cannot name a prior inventor as requested by the Examiner.

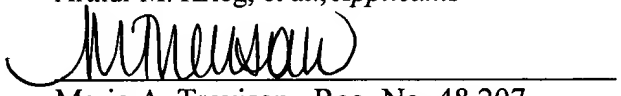
Identification of Further Applications:

The Examiner has required Applicants to "identify those Applications .. which are drawn to an invention not patentably distinct" from any amended claims presented by Applicants in response to the instant Office Action, and to file terminal disclaimers as appropriate. Applicants have identified (and will continue to identify) all co-pending applications of which they are aware to the Examiner in Information Disclosure Statements. Applicants have further amended the present claims in a manner that Applicants believe to be patentable. If the Examiner raises further rejections in view of co-pending applications, Applicants will address those rejections accordingly.

Summary

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance or has any questions or comments, he is requested to call the Applicants' representative at the telephone number listed below.

Respectfully submitted,
Arthur M. Krieg, et al., *Applicants*



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